TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
C1-A0315P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/014935	08.10.2004	09.10.2003

International Patent Classification (IPC) or national classification and IPC

C07K16/00, A61K9/08, 39/395, 47/02 , 47/18, 47/26, A61P35/00

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☒ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      1 flexible disk , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language: _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/Figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing (*specify*): _____

☐ any table(s) related to sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 5-8, 12-35

because:

☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 5-8, 12-35

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. IV **Lack of unity of invention**

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:
   - ☐ complied with.
   - ☒ not complied with for the following reasons:

The feature that is common to claims 1 to 35 is the stabilization of a high-concentration IgM solution.

As a result of the search, however, it was revealed that the document JP 2001-504092 A ((Rotkreuzstifung Zentrallaboratonum Blutspendedienst SRK), 27 March 2001) discloses a stabilized solution with a high concentration of IgM, which is to say that the document in question discloses the abovementioned common feature; consequently, it is apparent that said common feature is not novel.

For this reason, the stabilization of a high-concentration IgM solution does not define a contribution over the prior art, and thus said common feature cannot be a special technical feature.

[Refer to the Supplemental Box]

4. Consequently, this report has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-4, 9-11

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-4, 9-11	NO
Inventive step (IS)	Claims		YES
	Claims	1-4, 9-11	NO
Industrial applicability (IA)	Claims	1-4, 9-11	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Documents 1 to 6, indicated below, are cited in the international search report.

Document 1: JP 2001-504092 A (Rotkreuzstifung Zentrallaboratorium Blutspendedienst SRK), 27 March 2001

Document 2: JP 9-127114 A (Damabot Co., Ltd.), 16 May 1997

Document 3: JP 9-127112 A (Damabot Co., Ltd.), 16 May 1997

Document 4: JP 2-786335 A (Biotest Wolfram), 19 March 1990

Document 5: JP 2-493 A (Miles Inc.), 05 January 1990

Document 6: Pharm. Res., 1994, Vol. 11, No. 5, page 624 to 632

The inventions set forth in claims 1 to 4 and 9 lack novelty and do not involve an inventive step in the light of document 1.

Document 1 discloses a highly purified IgM concentrate for therapy and prophylaxis, wherein said purified IgM concentrate, which has a protein concentration of 5% and a pH level of 4.5, is the end

product from a process for eluting and then concentrating an IgM fraction (refer to claim 7, example 1 and the like). Therein, the end product disclosed in document 1 is considered to be the same as the solution with a high-concentration of stabilized IgM from the inventions set forth in the abovementioned claims.

The inventions set forth in claims 1, 3 and 10 lack novelty and do not involve an inventive step in the light of document 2.

Document 2 discloses an IgM-containing aqueous solution that has been stabilized by means of a bovine serum albumin solution, wherein said IgM-containing aqueous solution is obtained by using a tris-hydrochloric acid buffer solution (with a pH level of 8.5) that includes bovine serum albumin in order to dilute a commercial human IgM solution (to a concentration of 75 μg/ml of IgM); furthermore, document 2 also presents the results from tests for determining the stability of said solution over time (refer to example 1 and fig. 1). Therein, the IgM-containing aqueous solution that has been stabilized by means of a bovine serum albumin solution from the invention disclosed in document 2 is considered to be the same as the solution with a high-concentration of stabilized IgM from the inventions set forth in the abovementioned claims.

The inventions set forth in claims 1, 3, 10 and 11 lack novelty and do not involve an inventive step in the light of document 3.

Document 3 discloses a human IgM reagent that is obtained by using a tris-hydrochloric acid buffer solution (with a pH level of 8.5) in order to dilute modified IgM, which was created from a commercial human

IgM solution by means of a chemical reaction, to a concentration of 75 µg/ml; furthermore, document 3 also presents the results from tests for determining the stability of said solution over time (refer to example 1 and fig. 1).

Therein, the human IgM reagent disclosed in document 3 is considered to be the same as the solution with a high-concentration of stabilized IgM from the inventions set forth in the abovementioned claims.

The inventions set forth in claims 1 to 4 lack novelty and do not involve an inventive step in the light of document 4.

Document 4 discloses an IgM antibody preparation (i.e. an IgM concentrate) for intravenous administration, which is stable in an aqueous solution, and also presents the composition of said IgM concentrate (refer to table 1). In addition, document 1 further indicates that said IgM concentrate is thermostable in a 1.6% solution (i.e. a solution comprising 1.2 g/100 ml of IgM).

Therein, the 1.6% solution of the IgM concentrate disclosed in document 4 is considered to be the same as the solution with a high-concentration of stabilized IgM from the inventions set forth in the abovementioned claims.

The inventions set forth in claims 1 to 4, 9 and 10 lack novelty and do not involve an inventive step in the light of document 5.

Document 5 discloses a pure, stabilized IgM antibody preparation; indicates that said preparation can be used in therapy; and further indicates that the preparation in question is stabilized by maintaining the IgM at a concentration ranging from 0.01 to 50.00 mg/ml

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

and a pH level ranging from 4 to 10 while in the presence of NaCl and albumin, which serve as stabilizers. In addition, document 5 also indicates that the preparations in question remain clear without precipitation for a year or more at a temperature of 5°C (refer to the claims and the example in the upper right column of page 5).

Therein, the IgM antibody preparations disclosed in document 5 are considered to be the same as the solution with a high-concentration of stabilized IgM from the inventions set forth in the abovementioned claims; furthermore, said preparation is considered to be substantially free of human proteins other than IgM.

The inventions set forth in claims 1 to 4 and 9 to 11 lack novelty and do not involve an inventive step in the light of document 6.

Document 6 presents a solution with a 1 mg/ml concentration of IgM antibodies (4B9), and indicates that it was possible to increase the thermostability of said solution at a temperature of 50°C by adding a PVP or the like thereto (refer to page 625, right column, lines 15 to 42 and fig. 2).

Therein, the solution with a 1 mg/ml concentration of IgM antibodies (4B9) from the invention disclosed in document 6 is considered to be the same as the solution with a high-concentration of stabilized IgM from the inventions set forth in the abovementioned claims.

The inventions set forth in claims 2 and 9 do not involve an inventive step in the light of documents 2 and 3.

A person skilled in the art could adjust the dilution ratio and the pH level when preparing the IgM-containing aqueous solution that has been stabilized by

means of a bovine serum albumin solution from the invention disclosed in document 2, or when preparing the human IgM reagent from the invention disclosed in document 3, as appropriate.

The invention set forth in claim 9 does not involve an inventive step in the light of document 4.

The fact that the stability of a protein solution is affected by the pH level thereof is well known to a person skilled in the art. Such being the case, a person skilled in the art could have adjusted the pH level of a 1.6% solution of the IgM concentrate disclosed in document 4 in an appropriate manner in order to improve the stability thereof.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The standards of reference for the disclosures "high-concentration" and "stable," as set forth in claim 1, are unclear. Such being the case, the scope of the solution set forth in claim 1 is unclear.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material
      - [x] a sequence listing
      - [ ] table(s) related to the sequence listing

   b. format of material
      - [ ] in written format
      - [x] in computer readable form

   c. time of filing/furnishing
      - [ ] contained in the international application as filed
      - [x] filed together with the international application in computer readable form
      - [ ] furnished subsequently to this Authority for the purposes of search and/or examination
      - [ ] received by this Authority as an amendment* on _____

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box IV.3

Such being the case, the inventions set forth in claims 1 to 35 can be divided into the following groups of inventions: a group comprising the inventions set forth in claims 1 to 4 and 9 to 11, which are related to a solution with a high-concentration of stabilized immunoglobulin wherein the immunoglobulin is IgM; a group comprising the inventions set forth in claims 5 to 8, 13 to 22 and 24 to 34, which are characterized by the inclusion of multivalent cationic ions in a high-concentration IgM solution; and a group comprising the inventions set forth in claims 12, 23 and 35, which are characterized by the freezing or the freeze drying of a high-concentration stabilized IgM solution

Consequently, claims 1 to 35 do not have a novel special technical feature in common, and thus the present application cannot be considered to conform to the requirement of unity of invention (PCT Rule 13 (PCT Rule 13.1, 13.2 and 13.2)).